

# Osteoclast-Like Giant Cells: Focus on Entities Relevant to Dermatopathology and Underlying Pathogenesis

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**Abstract:** Osteoclast-like giant cells (OLGCs) resemble osteoclasts with their abundant cytoplasm and well-developed organelles. OLGCs are characteristic features of giant cell tumor of the tendon sheath and giant cell tumor of soft tissue but they have also been described in numerous other cutaneous conditions. The diagnostic and prognostic significance of the presence of OLGCs is unknown. Here, we summarize the clinical entities that can exhibit these cells to avoid a histological overlap, affecting diagnosis and management.

**Key Words:** osteoclasts, osteoclast-like giant cells, giant cells, multinucleated cells

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## LEARNING OBJECTIVES

After participating in this activity, physicians should be better able to:

1. Describe the main features of osteoclast-like giant cells compared with other giant cell types;
2. Identify the main tumors that can exhibit osteoclast-like giant cells on microscopy
3. Explain the possible source of the osteoclast-like giant cells.

## INTRODUCTION

Recognizing histopathological clues allows the pathologist to classify various clinical entities. Multinucleated giant cells (MGCs) are observed in a variety of pathological conditions and are one of the features that aid in diagnosis and disease classification.<sup>1</sup> They are differentiated based on morphology, association with various disease states, location, prevalence in various tissues, and stimuli that induce their formation and function. There are 3 types of giant cells seen

in inflammatory conditions. These are Langhans, foreign body, and Touton giant cells (Fig. 1). Langhans giant cells have a ring of nuclei at the periphery arranged in a horseshoe pattern; foreign body giant cells have nuclei that are haphazardly arranged throughout the cytoplasm, whereas Touton giant cells have annular grouping of nuclei similar to Langhans giant cells with amphophilic (blue–grey, granular) cytoplasm centrally, and pale, foamy cytoplasm at the periphery of the cell outside the nuclei.<sup>2</sup> A fourth type of giant cell is seen in benign and malignant neoplastic conditions and can be called osteoclast-like giant cells. Osteoclast-like giant cells (OLGCs) share a similar morphology to osteoclasts with their large multinucleated eosinophilic cytoplasm and numerous oval nuclei with prominent nucleoli.<sup>3</sup> In this review, we will focus on OLGCs.

Despite the collective effort to histologically define MGCs into various types, relying solely on morphologic characteristics is of limited value.<sup>4</sup> Molecular markers are vital in specifying the formation and function of these cells. MGCs form from various types of monocyte fusion/differentiation.<sup>4</sup> Monocyte fusion occurs in 3 discrete stages; fusion competency, migration, and cytoplasmic sharing. For fusion of cells to occur, they must express adhesion molecules (fusogens) to enable cell membrane approximation and cell machinery preparation. One of the important fusogens in OLGCs formation is dendritic cell-specific transmembrane protein (DC-STAMP). It is a transmembrane protein that leads to intracellular signaling responsible for osteoclastogenesis. Other involved fusogens include E-cadherin, macrophage fusion receptor-CD47 complex, and the mannose receptor CD206. These fusogens are not restricted to OLGCs formation; DC-STAMP and mannose receptor can be involved in Langerhan and foreign body giant cell formation as well.<sup>4</sup>

There are gaps in understanding the formation of MGCs, specifically the molecular determinants of cell fusion. Consequently, it is naïve to characterize MGCs using only histological attributes; however, acknowledging the presence of these cells can better elucidate their role in disease pathogenesis and may have possible clinical implications. In dermatology, OLGCs have been observed in a wide range of neoplasms. This review aims at summarizing these entities and the associated pathogenesis (Table 1).<sup>5</sup>

## PATHOGENESIS

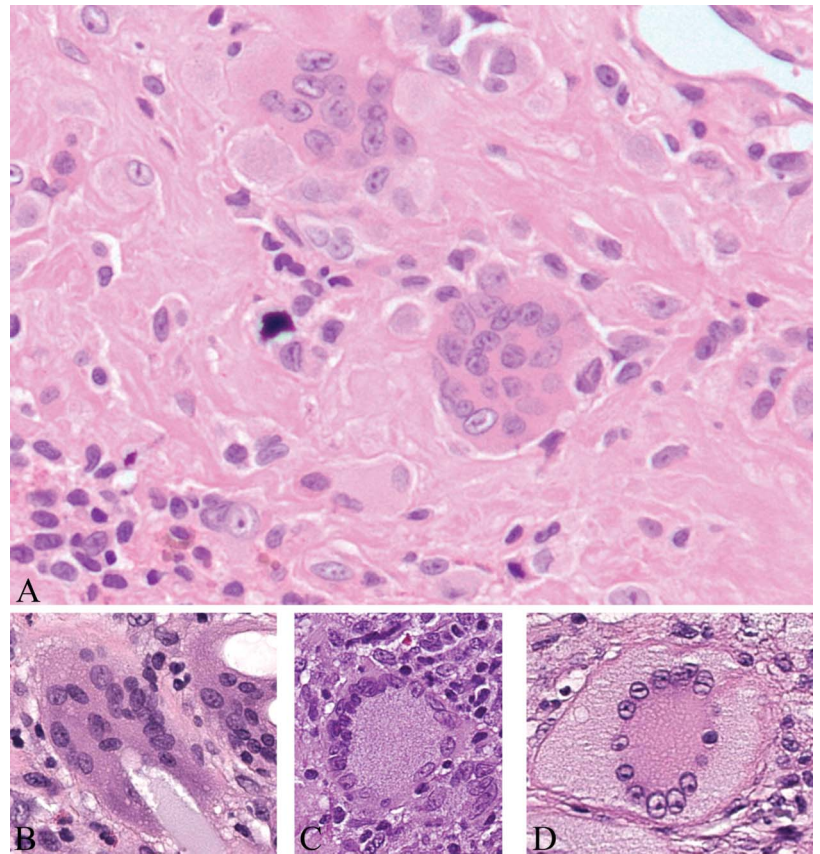
Bone tissue undergoes continuous resorption and formation by osteoclasts and osteoblasts respectively.<sup>6</sup> Osteoclasts are hematopoietic lineage cells that form from

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**FIGURE 1.** A, Osteoclast-like giant cells versus (B) foreign body, (C) Langhans, and (D) Touton giant cells (H&E A:  $\times 400$ ; B  $\times 400$ ; C  $\times 400$ , D  $\times 400$ ).

hematopoietic stems cells in the bone marrow. The hematopoietic stems cells form multipotent progenitor cells from which common myeloid progenitor cells, osteoclast progenitor cells, and finally osteoclasts originate.<sup>6</sup> The specific expression pattern of cell surface markers determines the fate of the common progenitor cell; forming either macrophages, dendritic cells (DCs), or osteoclasts. The relationship between macrophages and osteoclasts is intriguing. They are competing differentiation outcomes from the common myeloid progenitor cells and interact with each other by complex molecular mechanisms.<sup>7</sup> This interaction can be either stimulatory or inhibitory. The interplay between the immune and bone system is fairly dependent on the intricate balance between Th1 and Th2 cytokines.<sup>7</sup> Moreover, osteoclasts and macrophages share many common antigens such as CD45, CD68, and CD14. The latter is lost during the differentiation of the committed osteoclast.<sup>4</sup> To add to the complexity of osteoclastogenesis, there are reports of immature DCs *trans*-differentiation into CD14, CD1a, and RANKL positive osteoclasts under inflammatory conditions, suggesting that these cells can also be osteoclast progenitors.<sup>6,8</sup> The significance of this finding under physiologic conditions is not fully understood.<sup>6</sup>

The formation of osteoclasts from their precursors is regulated by the expression of 2 main cytokines; macrophage-colony stimulating factor (M-CSF) and receptor activator of NF- $\kappa$ B ligand (RANKL).<sup>9</sup> RANKL acts through its signaling

receptor, receptor activator of nuclear factor kappa-B (RANK); their interaction results in the activation of NFATc1 which in turn regulates osteoclastogenesis.<sup>6</sup> Once formed, the osteoclasts start creating microscopic trenches by secreting proteases and hydrochloric acid dissolving the bone matrix and minerals.<sup>9</sup> To equilibrate this activity, osteoprotegerin (OPG), a decoy receptor for RANKL, is typically secreted as an osteoclastogenesis inhibitory factor.<sup>6</sup> The OLGs are speculated to form under similar conditions and occasionally share similar osteoclastic functional properties.<sup>5</sup>

In a bid to understand the source of these OLGs, authors have been looking for similarities with normal osteoclast formation.<sup>5</sup> As mentioned, MGCs including osteoclasts are derived from the fusion of monocyte/macrophage lineage cells. The local environmental factors are major determinants of the fate of the progenitor cells. In the formation of OLGs, various molecules were consistently found in the microenvironment, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\alpha$  (IL-1 $\alpha$ ), RANKL, and M-CSF. All the aforementioned factors are crucial in osteoclast formation and may similarly contribute to the fusion of the monocyte-macrophage precursors forming OLGs.<sup>5</sup>

Langerhans cell histiocytosis (LCH) is one of the disorders that can exhibit OLGs. Up-close, CD1a<sup>+</sup> LCH cells were found to express RANK, whereas the local T cells and CD1a<sup>+</sup> LCH cells were immunoreactive to RANKL. Furthermore, M-CSF; a factor involved in the

**TABLE 1.** The Differential Diagnosis of Cutaneous Lesions With Osteoclast-like Giant Cells With the Respective Phenotypic Markers and Speculated Mechanisms of Formation

Entities Exhibiting OLGs on Microscopy		
Disease	Phenotypic Markers	Mechanism of Formation
Entities consistently exhibiting OLGs		
GCTTS	CD68 <sup>+</sup> , TRAP <sup>+</sup> , vitronectin Receptor <sup>+13,14</sup>	OLGCs are recruited into these lesions by RANKL expression in the neoplastic synoviocytes <sup>14</sup>
GCT-ST	CD68 <sup>+</sup> , SMA <sup>-</sup>	Histiocytic origin and are reactive in nature. Controversial.
Plexiform fibrohistiocytic tumor	CD68 <sup>+</sup>	—
Cutaneous osteosarcoma	—	—
Entities uncommonly exhibiting OLGs		
AFX	KP-1 <sup>+</sup> , RANK <sup>+</sup> , ±CD68 <sup>+</sup>	Macrophage-derived OLGs
LCH	Vitronectin <sup>+</sup> , TRAP <sup>+</sup> , MMP-9 <sup>+</sup> , cathepsin K <sup>+</sup> , CD68 <sup>+</sup>	Fusion of local myeloid progenitor cells forms OLGs
Entities rarely exhibiting OLGs		
Melanoma	HMB-45 <sup>+</sup> , Melan-A <sup>+</sup> , MITF <sup>+</sup> , S100 <sup>+</sup> CD68 <sup>+</sup> , CD163 <sup>+</sup> , alkaline phosphatase <sup>+</sup>	OLGCs are neoplastic melanocytes undergoing osteoclastic differentiation <sup>32</sup>
Intradermal nevus	MART1 <sup>+</sup> , S100 <sup>+</sup> , SOX10 <sup>+</sup> , CD68 <sup>-</sup>	Melanocytes which morphologically look like OLGs <sup>34</sup>
Squamous cell carcinoma	CD68 <sup>+</sup>	Controversial
BCC	CD68 <sup>+</sup>	Controversial
Primary CCS	CD68 <sup>+</sup> , AE1/AE3 <sup>-</sup>	Collision of 2 distinct tumors/transdifferentiation of stromal cells/induction by tumor microenvironment. <sup>51</sup>
DF	CD68 <sup>+</sup>	Reactive response
JHF	CD68 <sup>+</sup>	—
JXG	CD68 <sup>+</sup>	—
Soft tissue/mesenchymal tumors	CD68 <sup>+</sup> (leiomyosarcoma, chondroid lipoma), SMA <sup>-</sup> , desmin <sup>-</sup> , h-caldesmon <sup>-</sup> (leiomyosarcoma)	OLGCs result from the fusion/differentiation of tumor-associated macrophages
Nephrogenic fibrosing dermatopathy	Vitronectin receptor <sup>+</sup> , calcitonin receptor <sup>+</sup> , TRAP <sup>+</sup>	Fusion of macrophages?

differentiation of osteoclasts and generally produced by osteoblasts and stromal cells was highly expressed by MGCs.<sup>5</sup> Overall, these factors contribute to osteoclastogenesis and can imply that the OLGs have formed from the fusion of local myeloid progenitor cells rather than the migration of osteoclasts from the circulation.

Studies exploring the local factors which encourage OLGs formation highlighted the importance of osteopontin (OPN).<sup>10</sup> It is a phospho-glycoprotein involved in bone resorption by osteoclasts and is hypothesized to be involved in immune-related diseases such as rheumatoid arthritis and LCH.<sup>10</sup> Antigen presenting cells such as DCs and macrophages secrete OPN which in turn acts in an autocrine and paracrine manner, encouraging the secretion of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\alpha$ ). These factors potentiate the formation of OLGs. Clinical experiments on mouse models of collagen-induced arthritis, OPN deficiency prevented arthritis and anti-OPN was shown to be effective in preventing disease progression. In other experiments, blocking OPN from its receptors decreased the formation of OLGs.<sup>10</sup> This highlights the importance of the appropriate

environment and the presence of the right precursor cells contribute to the reactive formation of these cells through cellular fusion.<sup>8,10</sup>

In addition, OLGs express histiocytic surface markers such as CD68 and are negative for proliferative markers such as Ki-67. This further supports the formation of OLGs by the fusion of their macrophage precursors rather than cell division.<sup>8</sup>

On the other hand, many authors believe that the presence of OLGs in tumor microenvironment points to a neoplastic origin these giant cells may be formed through tumor cell division.<sup>11</sup> In atypical fibroxanthoma (AFX), the OLGs are almost always intimately associated with atypical large pleomorphic, multinucleated cells. These cells were inconsistently CD68<sup>+</sup>, but were immunoreactive to anti-RANK. Combining these findings, the authors suggest that OLGs could be an extreme step of differentiation of the neoplastic pleomorphic cells. In addition, TGF- $\beta$ , IL-1, and osteoprotegrin released from tumor microenvironment or from the local inflammatory cells promoted this neoplastic osteoclastic differentiation. To counter argue the absence of

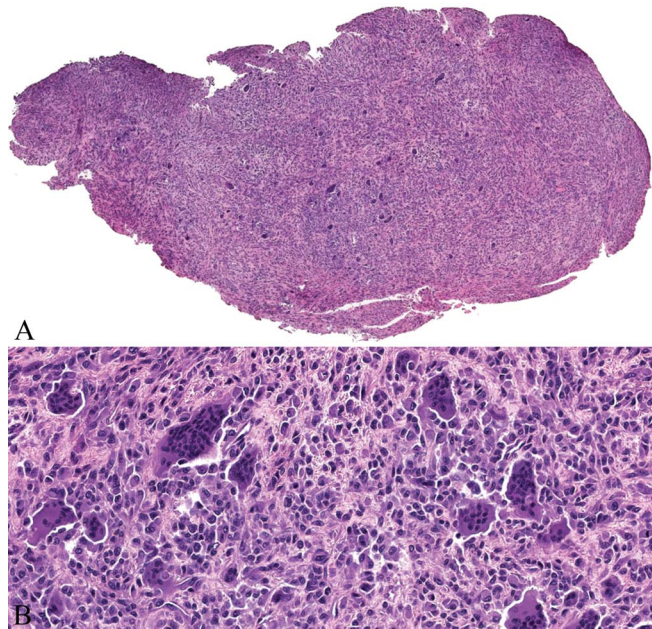
proliferative markers such as Ki-67, it is hypothesized that these mature cancer cells are too differentiated to proliferate as OLGs.<sup>11</sup>

In brief, conclusive evidence is still lacking in support of the reactive versus neoplastic origin of OLGs.<sup>5</sup> In this review, we find the reactive formation of these cells to be more plausible in the light of the available studies. Nonetheless, acquainting the dermatopathologists to the presence of OLGs in the summarized entities can assist in tracing the origin of these cells in the future.

## ENTITIES COMMONLY EXHIBITING OLGs

### Giant Cell Tumor of the Tendon Sheath (GCTTS)

GCTTS is a benign, slowly growing soft tissue tumor originating from synoviocytes.<sup>12</sup> Clinically, it can be divided into localized and diffuse forms based on the growth pattern. Localized GCTTS presents as a nodular lesion mainly on digits, whereas the diffuse form occurs adjacent to larger weight-bearing joints.<sup>12</sup> Histologically, GCTTS is composed of 2 predominant types of cells (Fig. 2); monocyctic polyhedral stromal cells (MCs) and MGCs.<sup>13</sup> The MGCs have a characteristic osteoclast-like appearance. They are scattered throughout the lesions and are typically numerous, but can be sparse in highly cellular lesions and absent in rare cases.<sup>14</sup> Phenotyping these cells using various immunohistochemical stains identified CD68<sup>+</sup> OLGs in contrast to the large mononuclear neoplastic synoviocytes, which are desmin and RANKL immunoreactive.<sup>13,14</sup> In these studies, the MCs were CD68<sup>+</sup>, CD163/Cd11c<sup>+</sup>, HAM56<sup>+</sup> (80%) and vimentin<sup>+</sup>; typical histiocytic markers.<sup>13,14</sup>



**FIGURE 2.** Giant cell tumor of tendon sheath with OLGs (H&E A:  $\times 40$ ; B  $\times 200$ ).

The pathogenesis of GCTTS is unclear.<sup>12</sup> It is common to find gains of chromosomes 5 and 7, and gene rearrangements of 1p11-13. One of the implicated genes is *CSF1*. It has been traced to 1p13-21 which encodes for the colony-stimulating factor 1 (CSF1) protein, involved in macrophage function, differentiation, and proliferation. CSF1 has been noted to be central to the GCTTS pathogenesis. Most MCs and MGCs express CSF1 receptor, suggesting the possibility that aberrant CSF expression by GCTTS synoviocytes can prime the tumor field to recruit reactive inflammatory cells such as OLGs.<sup>14</sup>

In an attempt to understand the etiology of GCTTS, studies were performed to trace the lineage of the constituent cells. One finding was that the MGCs and MCs are tartrate-resistant acid phosphatase<sup>+</sup> (TRAP) and vitronectin receptor<sup>+</sup>. Both these markers are distinctive of osteoclasts, but not specific.<sup>13</sup> Moreover, calcitonin receptor (CTR), which is a definitive marker to distinguish osteoclasts from other hematopoietic derived cells was found to be expressed on the MCs before fusion and formation of OLGs.<sup>15</sup> Other studies showed that the OLGs in GCTTS had a similar enzymatic content and distribution when compared with osteoclasts. They were rich in acid phosphatase and were able to form pits when isolated and placed with cortical bone slices, highlighting their bone resorption ability.<sup>13,16</sup> However, these findings still fail to identify a definitive origin of the MGCs.

### Giant Cell Tumor of Soft Tissue

Giant cell tumor of soft tissue (GCT-ST) is a rare, well-defined, slow-growing, superficial tumor, most often involving the lower extremities and trunk. The histogenesis of GCT-ST is unclear. Because of its unpredictable behavior, some suggest a clinical and histological spectrum from low-grade to high-grade malignant behavior; differentiated by the degree of atypia, pleomorphism, and mitotic activity.<sup>17</sup> Many consider the high-grade malignant GCT-ST as a histological variant of pleomorphic dermal sarcoma (PDS) or fibrosarcoma with osteoclastic differentiation.<sup>18</sup>

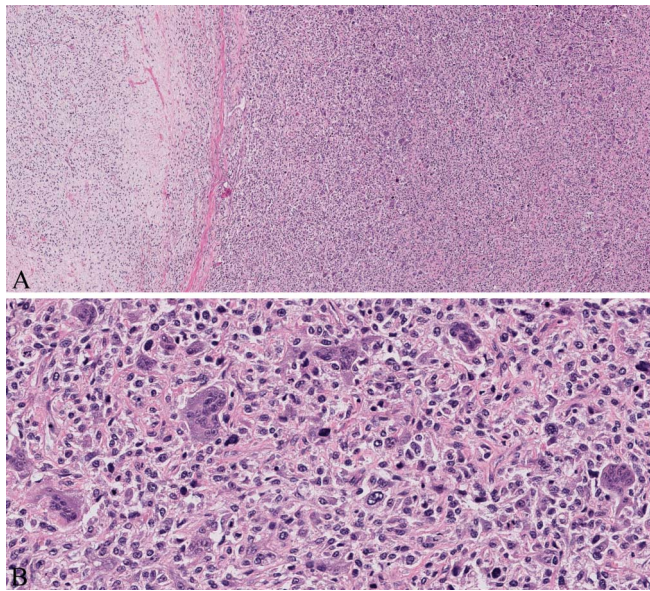
On histology, there is a mixture of round to oval mononuclear cells and multinucleated osteoclastic giant cells, immersed in a richly vascularized stroma (Fig. 3). Bone tissue formation is seen in about half of the tumors and is mostly located at the periphery of the lesion.<sup>19,20</sup>

When comparing GCT of soft tissue to GCTTS, GCTTS displays more clustered OLGs, a more uniform distribution of mononuclear cells with well-defined cell membranes. In addition, GCTTS exhibits well-distributed collagen outlining individual cells or groups of cells in contrast to the broad strands of collagen in GCT of soft tissue resulting in its characteristic multinodular morphology. In addition, GCT of soft tissue is more likely to exhibit cystic change and reactive bone formation.<sup>21</sup>

### Plexiform Fibrohistiocytic Tumors (PFHTs)

PFHTs are low-grade malignant soft tissue tumors that are typically located in the superficial subcutaneous layer of the upper extremities.<sup>21</sup> They are peculiar in their poorly demarcated but multinodular nature; each tumor nodule is composed of histiocytes, myofibroblasts, and OLGs.<sup>22,23</sup>

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**FIGURE 3.** Giant cell tumor of soft tissue with OLGCs (H&E A:  $\times 40$ ; B  $\times 200$ ).

Each nodule is comparable to giant cell tumor of soft tissue, despite some differences. In PFHT, the nodules are smaller, separated by fatty tissue, accompanied by spindle cells rich in collagen and they also lack the storiform spindle cell arrangement found in giant cell tumor of soft tissue.<sup>21</sup>

The pathogenesis of PFHT is unknown. It can either be predominantly histiocytic or fibroblastic or mixed, with CD68<sup>+</sup> MGCs and SMA<sup>+</sup> fibroblasts.<sup>22</sup> The OLGCs occur more commonly in the histiocytic subtype and have been reported to be absent in rare cases of PFHTs.<sup>23</sup>

### Cutaneous Osteosarcoma

Cutaneous osteosarcoma is a rare malignant tumor associated with a poor prognosis, often resulting in metastasis and death. Clinically, it presents as fast-growing exophytic ulcerated nodules.<sup>24,25</sup> Cutaneous osteosarcoma does not arise from bone, but because of its deep nature, it can secondarily involve bone structures.<sup>25</sup>

Histologically, cutaneous osteosarcoma is characterized by proliferation of pleomorphic cells underneath epidermal ulceration with foci of osteoid and less frequently chondrocytic, teleangiectatic, or rhabdoid differentiation. Tumor cells are either spindle or polygonal cells that show an impressive degree of atypia and mitotic activity. These tumor cells surround the areas of ossification and are interspersed with

OLGCs. Immunohistochemical studies are nonspecific; staining for vimentin and sometimes osteonectin, hence, combining clinical, histological, and immunohistochemical studies is key to reach this diagnosis.<sup>24</sup>

## ENTITIES UNCOMMONLY EXHIBITING OLGCs

### AFX

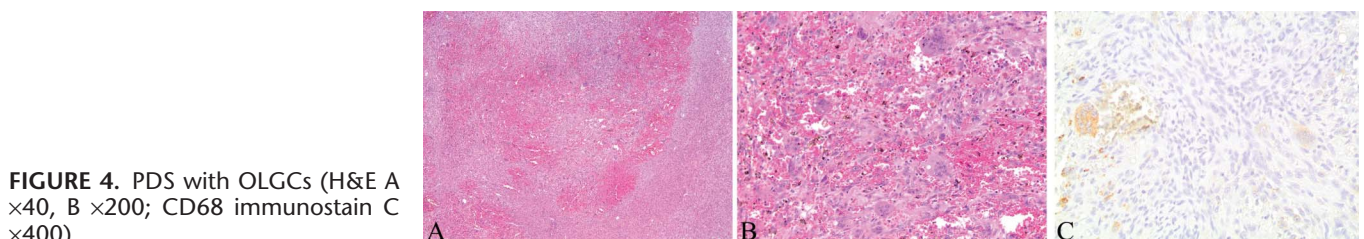
AFX is a mesenchymal tumor with fibrohistiocytic and occasionally myofibroblastic differentiation. AFX presents as a single nodule on the head and neck of the elderly with a possible local recurrence but low metastatic potential. AFX is considered a superficial variant of PDS, which is a rare dermal spindle cell tumor.<sup>26</sup> PDS has an associated variant that can display OLGCs (Fig. 4); however, these giant cells are uncommonly seen in AFX (Fig. 5).<sup>27</sup>

On histology, AFX presents as a well-circumscribed lesion with an epidermal collarette around pleomorphic spindle, epithelioid, and multinucleated cells. In a review of 66 AFX lesions, certain uncommon morphological changes were noted. These changes were either present focally or were the chief constituents of the tumor. The presence of OLGCs, and osteoid sclerosis were among these changes.<sup>28</sup> Osteoclast-like giant cells stained strongly for KP-1, a macrophage-associated antigen that distinguishes these cells from bone-marrow-derived osteoclasts.<sup>11,28</sup>

### Langerhans Cell Histiocytosis

LCH is a rare disease that ranges from localized lesions to fatal disseminated leukemia. It is characterized by the clonal proliferation of CD1a<sup>+</sup> Langerhans cells, and other myeloid-derived cells.<sup>5</sup> On histology, CD1a and langerin positivity typically confirm the diagnosis.<sup>29,30</sup>

Osteoclast-like giant cells in LCH are not only limited to the skin lesions but were also observed in lymph nodes (LNs) and the osteolytic bone lesions. The OLGCs stain for osteoclastic markers such as vitronectin, TRAP, MMP-9, and cathepsin K, the latter 3 involved in tissue degradation.<sup>5</sup> Osteoclast-like giant cells in osteitic and nonosteitic (skin, LNs) lesions are frequently CD68<sup>+</sup>, confirming their monocyte-macrophage origin. Looking at CD1a expressivity, the nonosteitic OLGCs were positive, whereas the osteitic lesions were not. This suggests that the OLGCs in skin and LNs could be forming from local CD1a<sup>+</sup> Langerhans cells, whereas osteitic OLGCs are derived from a different precursor population.<sup>5</sup>



**FIGURE 4.** PDS with OLGCs (H&E A:  $\times 40$ , B  $\times 200$ ; CD68 immunostain C  $\times 400$ ).



**FIGURE 5.** Atypical fibroxanthoma with OLGCs (H&E A:  $\times 40$ ; B  $\times 200$ ).

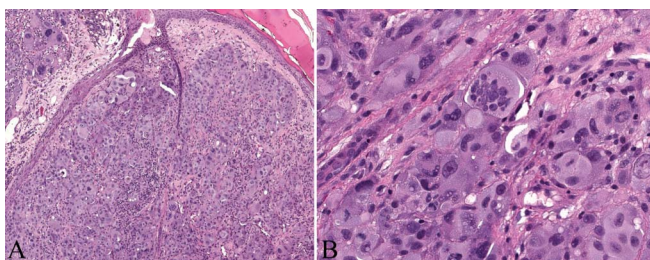
**ENTITIES RARELY EXHIBITING OLGCs**

**Nevi & Melanoma**

In melanoma, less than 10 cases associated with OLGCs have been reported.<sup>31</sup> The origin of these OLGCs is still controversial. In some reports, these cells express monocyte/macrophage lineage markers (such as CD68), but not melanocytic markers, implying that they are a reactive response to the neoplasm. Nevertheless, a recent report of metastatic melanoma to the lung reported the presence of OLGCs reactive to HMB-45, Melan-A, and S100 in addition to their OLGC histological profile (CD68, CD163, and alkaline phosphatase).<sup>32</sup> In addition, we have observed OLGC in focal areas of melanoma which are positive with melanoma markers (Fig. 6). Conceivably, many authors believe that the melanoma-associated OLGCs are truly neoplastic melanocytes undergoing osteoclastic differentiation.

Whether these OLGCs affect the tumor behavior is to be determined. Previous studies have shown that melanoma cells can induce the fusion of tumor-associated macrophages into OLGCs.<sup>33</sup> These OLGCs express an osteoclastic enzyme profile and can activate the RANK-RANKL pathway, which is normally used for the resorption of mineralized bone.<sup>31</sup> In some malignancies such as breast cancer, the activation of this pathway has been shown to encourage metastasis. Furthermore, the RANK expression is significantly increased in the peripheral circulating cells and metastasis in some patients with advanced melanoma.<sup>31</sup> Thus, it is possible that the OLGCs can contribute to the bone destruction in osteolytic metastasis and could perhaps play a role in the local invasion and involvement of other distant organs.<sup>33</sup> Despite these findings, the independent prognostic significance of the OLGCs still needs further validation because their presence is rare in melanoma.<sup>31</sup>

OLGCs have been recently reported in a case of an intradermal nevus. These OLGCs are nevus cells that retained their melanocytic immunoreactivity and were prominently negative for CD68.<sup>34</sup> We have seen similar cells in a compound melanocytic nevus (Fig. 7).



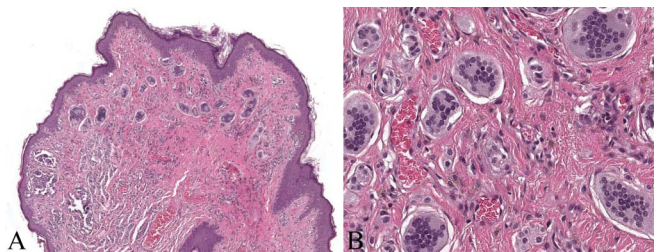
**FIGURE 6.** Melanoma with OLGCs (H&E A:  $\times 40$ ; B  $\times 200$ ).

**Nonmelanoma Skin Cancers & Primary Cutaneous Carcinosarcoma (CCS)**

Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC) are the most common malignancies of the skin.<sup>35,36</sup> SCCs and BCCs can portray variable stromal reactions, one of which is formation of a sarcomatoid stroma with OLGCs (Fig. 8). Some associate a more aggressive nature of these tumors in the presence of OLGCs.<sup>36</sup> The source of OLGCs is still controversial (reactive vs. neoplastic) and the sarcomatoid component can be easily mistaken for CCS.<sup>35</sup>

Carcinosarcoma is primarily a malignant tumor of the genitourinary tract and lung. The cutaneous counterpart is exceedingly rare and seems to be of better prognosis, but has a metastatic potential.<sup>37,38</sup> It is characterized by the admixture of epithelial and mesenchymal components. The epithelial component most commonly resembles a BCC or an SCC, but may also resemble malignant adnexal tumors. The mesenchymal component may resemble a chondrosarcoma, osteosarcoma, PDS, rhabdomyosarcoma, or fibrosarcoma.<sup>38</sup>

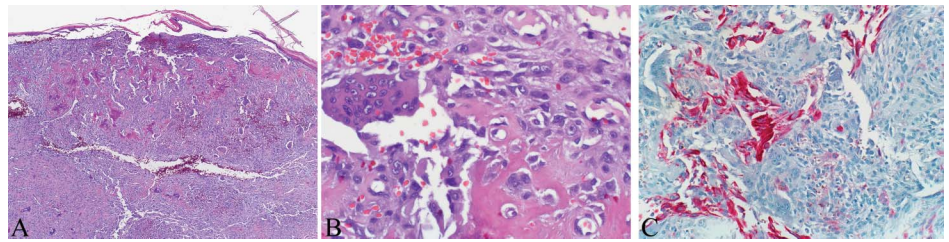
A clear distinction between SCCs and BCCs with OLGCs and CCS is absent. This is due to the lack of understanding of their pathogenesis. There are several hypotheses explaining the formation of CCS and have been extrapolated to clarify the presence of OLGCs in SCCs.<sup>36</sup> First is the “collision phenomenon” where 2 tumor types arising from 2 distinct progenitor cells are thought to merge together. The second is the “transdifferentiation” of a carcinoma subpopulation, thus acquiring a sarcomatoid phenotype. These 2 hypotheses attribute neoplastic characteristics to the OLGCs. A third theory is that tumor cells through cytokines and growth factors “induce” the pro-tumoral differentiation of stromal cells. The absence of p53 staining in the OLGCs despite the tumor cells being strongly immunoreactive supports this theory. However, some propose that the dedifferentiation of neoplastic cells results in the loss of p53 immunoreactivity.<sup>36</sup>



**FIGURE 7.** Dermal melanocytic nevus with OLGCs (H&E A:  $\times 40$ ; B  $\times 200$ ).

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**FIGURE 8.** Squamous cell carcinoma with OLGs (H&E A:  $\times 40$ ; B  $\times 200$ ). C, Immunostaining with high-molecular weight cytokeratin ( $\times 200$ ).



Many authors suggest assessing the presence and degree of atypia to differentiate CCS from the other entities. In general, the spindled stroma with OLGs in BCCs and SCCs portray a low mitotic index, lack the p53 and Ki-67 overexpression, necrosis and pleomorphism associated with CCS.<sup>36,39</sup> In CCS, the malignant features need to be present in both epithelial and mesenchymal components. Other authors report this distinction to be unambiguous and suggest a spectrum with increasing atypia in the stromal component, starting with epithelial tumors with reactive OLGs (absent or mild atypia) to CCS with obvious atypical mesenchymal component. Deep biopsies for appropriate histopathological examination are therefore important to distinguish these entities.<sup>39</sup>

### Dermatofibroma (DF)

DF is a common skin lesion, believed to be either an inflammatory/reactive entity or a benign neoplastic growth. It can present with many histopathological variants such as epithelioid, palisading, cellular, or sclerotic changes making the correct diagnosis difficult. One of these rare changes is the presence of OLGs.<sup>40</sup> Some authors agree with the reactive nature of these cells, in particular because of the hypothesized reactive nature of DFs.<sup>40</sup> Immunohistochemical studies are key in differentiating DF from other benign and malignant entities. CD68 is generally positive in most fibrohistiocytic cells and in the OLGs. The fibrohistiocytic cells are also positive for factor XIIIa.<sup>40</sup>

### Juvenile Hyaline Fibromatosis (JHF)

JHF is a rare familial disease with an autosomal recessive inheritance.<sup>41</sup> It is characterized clinically by abnormal growth of hyalinized fibrous tissue of the head and neck soft tissues mainly. JHF shows variable penetrance with some patients presenting with only skin and soft tissue nodules, whereas others can have multisystem involvement. Histologically, JHF is characterized by an increased fibroblast number embedded in hyalinized connective tissue stroma. In the stroma, there are interspersed mononuclear cells and there are rare reports of adjacent OLGs with occasional calcification.<sup>41</sup> The OLGs were positive for CD68 and negative for atypical features confirming their histiocytic origin.

### Juvenile Xanthogranuloma (JXG)

JXG is a benign non-Langerhans cell histiocytic tumor of the skin that typically occurs in the first 2 decades of life.<sup>42</sup> Histologically, JXG is characterized by mononucleated epithelioid cells, spindle-shaped fibroblasts, and foamy

macrophages (Touton giant cells). In some reports, on fine needle aspirate (FNA) biopsy and regular histological examination, additional features have been observed such as the OLGs. The foamy macrophages and the OLGs were positive for CD68.<sup>42</sup>

### Soft Tissue Mesenchymal Tumors

Histologically, some soft tissue mesenchymal tumors can also have OLGs closely mimicking PDS. One example is leiomyosarcoma.<sup>43</sup> Arising from smooth muscle, it is characterized by a distinctive fascicular growth pattern of spindle shaped cells with cigar-shaped nuclei. Nuclear atypia is conspicuous with the expression of smooth muscle markers; SMA, desmin, h-caldesmon.<sup>43,44</sup> The presence of OLGs is commonly seen in noncutaneous leiomyomas, but rarely found in the skin.<sup>45</sup> Studies have shown that the OLGs exhibit osteoclastic markers, are CD68 immunoreactive and are negative for smooth muscle markers.<sup>44</sup> Hence, it is theorized that the OLGs result from the fusion/differentiation of tumor-associated macrophages.<sup>44</sup>

Chondroid lipoma is a benign neoplasm defined by the histological presence of a well-circumscribed and lobulated growth of multivacuolated lipoblast-like cells and chondromyxoid matrix. Up-to-date, there has been only one report of chondroid lipoma with OLGs.<sup>46</sup> These cells were CD68 positive and aligned at the periphery of the tumor admixed with neoplastic cells.<sup>46</sup>

Other examples of a soft tissue mesenchymal tumor with OLGs are liposarcoma and malignant mesenchymoma.<sup>47,48</sup> MM is a rare tumor of the elderly, most often on the thighs and retroperitoneum. It is defined by the presence of at least 2 distinctive lines of mesenchymal differentiation. Most often mesenchymoma show an admixture of liposarcomatous, rhabdomyosarcomatous, and/or osteo/chondrosarcomatous elements. Occasionally there is unusual infiltration of OLGs.<sup>48</sup>

## MISCELLANEOUS INFLAMMATORY CONDITIONS

### Nephrogenic Fibrosing Dermopathy

The most prominent example of purely reactive conditions featuring OLGs is nephrogenic systemic fibrosis (NSF). NSF is a debilitating fibrosing illness characterized by significant skin thickening, mostly observed in patients with advanced renal insufficiency and has been associated with the use of gadolinium-based contrast agents.<sup>49</sup>

Histologically, NSF contains fibroblast-like cells, histiocytes embedded in thickened collagen. Rarely, OLGs and calcification can be observed, with an estimated incidence of 2%–5%. The OLGs express osteoclast markers; vitronectin receptor, calcitonin receptor, and TRAP. The mechanism of formation of these OLGs is unclear, but may reflect a chaotic matrix homeostasis induced by renal disease that can result in macrophage fusion.<sup>49,50</sup>

## CONCLUSIONS

OLGCS have been reported in a plethora of skin diseases. It is important to recognize the presence of such morphological changes to avoid diagnostic confusion. OLGs could be a characteristic finding in some cutaneous conditions, but it could be a nonspecific reaction to the lesion in others. OLGs are present in both benign and malignant lesions with unclear prognostic significance.<sup>28</sup> More aggressive behavior is reported in the presence of OLGs in some cases such as melanoma, BCC and SCC, whereas in some cases they are considered as benign spectator cells.<sup>31,36</sup>

The presence of OLGs in tumors can have therapeutic implications. For example, in melanoma, Zoledronate (bisphosphonate) and Denosumab (RANKL inhibitor) have been found to be effective in controlling tumor metastasis, particularly to the lung.<sup>31</sup> Denosumab mainly works by reducing the number of RANK-positive OLGs and mononuclear stromal cells which overexpress RANKL; both crucial components in the summarized entities.<sup>5</sup> This highlights the necessity of understanding OLGs and their role in disease pathogenesis in the hope of using this understanding in forming diagnostic criteria and possible therapeutic strategies.

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CME EXAMINATION  
March 2021

Please mark your answers on the ANSWER SHEET.

After participating in this activity, physicians should be better able to: 1. Describe the main features of osteoclast-like giant cells compared to other giant cell types; 2. Identify the main tumors which can exhibit osteoclast-like giant cells on microscopy. 3. Explain the possible source of the osteoclast-like giant cells.

## CME QUESTIONS

- Giant cell tumor of the tendon sheath arises from which cell type?
  - Osteoclasts
  - Fibroblasts
  - Macrophages
  - Synoviocytes
  - Osteoblasts
- Which of the following statements is false?
  - The presence of osteoclast-like giant cells can affect the metastatic potential of tumors.
  - Osteoclast-like giant cells is not present in inflammatory conditions.
  - Osteoprotegerin has high affinity to RANKL.
  - Osteopontin is a pro-inflammatory phospho-glycoprotein.
  - M-CSF can be secreted by osteoblasts.
- Which of the following is involved in the pathogenesis of giant cell tumor of the tendon sheath?
  - p53
  - CSF1
  - p16
  - ECM1
  - FGF
- Which of the following factors inhibits osteoclastogenesis?
  - Receptor activator of nuclear factor kappa-B (RANK)
  - Receptor activator of NF-κB ligand (RANKL)
  - Osteoprotegerin
  - Tumor necrosis factor-α
  - M-CSF
- Which receptor is used to define macrophage-derived osteoclasts and not regular osteoclasts?
  - CD20
  - CD14
  - S100
  - CD56
  - CD4

